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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
COTTON, ABIGAIL MANDA

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,405	CHANDRASEKAR ET AL.	
	Examiner	Art Unit	
	Abigail M. Cotton	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/23/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the amendment submitted on January 23, 2006. Claims 1-23 are pending in the application, with claims 9-23 having been newly added. Accordingly, claims 1-23 are being examined on the merits herein.

The rejection of claims 1-8 under 35 U.S.C. 101 and 112, second paragraph, for reciting a "use" of the invention, is being withdrawn in view of Applicant's amendments to the claims to positively recite a method for improving reendothelization and vascular endothelial function comprising administering 17-beta estradiol or a derivative thereof.

The rejection of claims 1-8 under 35 U.S.C. 112, second paragraph, as being indefinite because it was not clear whether a method of using or making was being claimed, is being withdrawn in view of Applicant's amendments to the claims to positively recite a method of use comprising administration of the compound as claimed.

The rejection of claim 5 under 35 U.S.C. 112 second paragraph, as lacking antecedent basis for the term "said pharmaceutically acceptable carrier" is being withdrawn in view of Applicant's amendment to the claims to provide proper antecedent basis for the term.

Applicant's arguments filed January 23, 2006 regarding the rejection of the claims over the prior art have been fully considered but they are not persuasive.

The claims are rejected as follows.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as lacking proper antecedent basis for the term "the injured site" as recited in the claim. The claim refers to improving reendothelization and vascular endothelial function in a patient, but does not indicate which "injured site" is being referred to. Thus, the metes and bounds of the claim are not clear, and the claim is indefinite under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 8-9, 14 and 18-19 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,866,561 to Mark T. Ungs, issued February 2, 1999.

Ungs teaches a method for inducing angiogenesis in blood vessels proximal to stenosed regions, including application of an estrogen compound to the blood vessel walls at a treatment site proximal to or upstream of the stenosis (see abstract, in particular.) Ungs teaches that restenosis following PTCA is a signification problem, and that administration of estrogen to the stenosed, dilated region after PTCA has been suggested for the purposes of preventing restenosis (see column 1, lines 10-20 and 40-52, in particular), and thus teaches administration to an injured site, i.e. one that has been injured by PTCA. Ungs teaches that it is thus desirable to increase perfusion to heart tissue in place of or in addition to PTCA treatment (see column 1, lines 54-65, in particular.) Ungs teaches that a preferred method of treating stenosis involves application with a double walled drug delivery balloon catheter, as well as by coating a stent with an estrogen compound or by puncturing a vessel wall (see column 2, lines 5-45, in particular.) Ungs teaches that preferred estrogen compounds include 17-Beta estradiol (see column 4, lines 1-12, in particular), as in claim 14. Accordingly, Ungs teaches administration of 17-Beta estradiol in the lumen of a blood vessel having suffered vascular injury. Ungs furthermore teaches single administration of 17-Beta

estradiol, as recited in claims 8 and 18, as Ungs teaches the compound can be administered via a stent or balloon catheter.

Regarding claims 9 and 19, Ungs teaches the estrogens such as 17-beta estradiol can be administered with a drug delivery balloon catheter or on a stent, as discussed above, and thus teaches administering the compound with a device.

It is respectfully pointed out that the recitation "for improving reendothelization and vascular endothelial function" in claim 1 has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *in re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152 88 USPQ 478, 481 (CCPA 1951.)

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12-13 and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,866,561 to Mark T. Ungs, issued February 2, 1999.

Ungs is applied as discussed for claims 1, 8-9, 14 and 18-19 above, and teaches administration of 17-beta estradiol in the lumen of a blood vessel having suffered vascular injury.

Ungs does not specifically teach a specific embodiment in which the 17-beta estradiol is administered following percutaneous transluminal coronary angioplasty, as recited in claims 12 and 22, or simultaneously with percutaneous transluminal coronary angioplasty (PTCA), as recited in claims 13 and 23.

However, Ungs does teach that restenosis following PTCA is a significant problem (see column 1, lines 10-20, in particular), and teaches that treatment to increase perfusion to heart tissue, such as with estrogen compounds, are desirably performed in place of, or in addition to, PTCA (see column 1, lines 50-65, in particular.) Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the 17-beta estradiol following or simultaneously with the PTCA, based on the teachings of Ungs, with the expectation of increasing perfusion to heart tissue and for reducing the likelihood of restenosis.

Claims 2-4 and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,866,561 to Mark T. Ungs, issued February 2, 1999, as applied to claims 1, 8-9, 12-14, 18-19 and 22-23 above, and further in view of U.S. Patent No. 5,512,557 to Peter Collins, issued April 30, 1996.

Ungs is applied as discussed above, and teaches administration of 17-Beta estradiol in the lumen of a blood vessel having suffered vascular injury. Ungs does not specifically teach administration in the unit doses recited in claims 2-4 and 15-17.

Collins teaches that 17-beta estradiol can be provided to treat coronary heart disease (see abstract, in particular.) Collins teaches that a suitable dose may be delivered in various forms, depending upon the route of administration, such as oral or parenteral administration (see column 2, lines 1-15, in particular) and the dosage may be varied according to the symptoms, age and body weight of the patient (see column 2, lines 15-25, in particular.) Collins teaches that a suitable daily dose may be from 0.5 mg to 2 mg (see column 2, lines 15-25.) Assuming administration of the dose to a female patient having a weight of about 65 Kg (~130 lbs), the dose is equivalent to a daily dose of about 8 micrograms/kg to about 30 micrograms/Kg, which meets and/or closely overlaps with the does ranges recited in the claims. Furthermore, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to optimize dose unit according to patient weight, means of administration, etc, in light of the teachings of Collins, to provide a desired dosage of the

17-B estradiol. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the dosage taught by Collins in the vascular injury treatment and estrogen delivery method of Ungs, because Collins teaches that the dose is capable of showing beneficial cardiovascular effects. Thus, one of ordinary skill in the art would have been motivated to deliver 17-beta estradiol by the method of Ungs and in the dosage of Collins, with the expectation of providing an effective dosage capable of yielding cardiovascular treatment.

Claims 5-7, 10-11 and 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,866,561 to Mark T. Ungs, issued February 2, 1999, as applied to claims 1, 8-9, 12-14, 18-19 and 22-23 above, and further in view of U.S. Patent No. 4,727,064 to Josef Pitha, issued February 23, 1998.

Ungs is applied as discussed above, and teaches administration of 17-Beta estradiol in the lumen of a blood vessel having suffered vascular injury, for example via catheter or a stent (see column 2, lines 5-45, in particular), as recited in claims 10-11 and 20-21. Ungs does not specifically teach administration of hydroxypropyl-beta-cyclodextrin (HPCD) as recited in claims 5-7. Ungs also does not specifically teach

providing a pharmaceutically acceptable carrier in administering the 17-beta estradiol via catheter or stent, as recited in claims 10-11 and 20-21.

Pitha teaches that pharmaceutical preparations containing cyclodextrin derivatives have enhanced dissolution properties and thus enhanced absorption by the body (see abstract, in particular.) Pitha teaches that cyclodextrin mixtures effectively solubilize liphophilic drugs in aqueous media (pharmaceutically acceptable carrier), and have low toxicity (see column 2, lines 35-60, in particular.) Pitha demonstrates that estradiol is a drug that exhibits improved solubility in combination with hydroxypropyl-beta-cyclodextrin (see Table I, in particular.) Accordingly, Pitha teaches the benefits in improved solubility and absorption of providing estradiol in combination with hydroxypropyl-beta-cyclodextrin, and in a pharmaceutically acceptable carrier such as aqueous media, as recited in claims 10-11 and 20-21 are known.

Regarding the dosage amount recited in claim 7, Pitha teaches that the cyclodextrin additives may generally be utilized in a weight percent of from about 40-60% of the drug solution (see column 2, lines 62-68, in particular.) Pitha furthermore teaches intraperitoneal injection of hydroxypropyl-beta-cyclodextrin into mice was non-fatal at 3.2g/kg, and teaches a lack of oral toxicity of the hydroxypropyl-beta-cyclodextrin (see column 4, line 64 through column 5, line 5, in particular.) Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to optimize the amount of hydroxypropyl-beta-cyclodextrin

provided in the medication, according to the guidelines provided by Pitha, to provide the desired solubility and absorption characteristics of the estradiol. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the hydroxypropyl-beta-cyclodextrin and pharmaceutically acceptable carrier of Pitha in the 17-beta estradiol delivery method of Ungs, with the expectation of improving the solubility and absorption of the 17-beta estradiol compound in the patient.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory

double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4 and 8-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 9-10 and 15-33 of copending Application No. 10/602,934, in view of U.S. Patent No. 5,866,561 to Ungs. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the co-pending application recite reducing restenosis in a patient having suffered vascular injury by administering an effective dose of 17beta-estradiol or derivative at an injured site in the lumen of a blood vessel of the patient, whereas the instant claims are to a method of using 17beta-estradiol or a derivative thereof to improve reendothelization and vascular endothelial function, by administering the compound at the injured site in the lumen of a blood vessel having suffered an injury. Ungs teaches that restenosis is linked to vascular endothelia growth (see column 1, lines 30-40, in particular.) Accordingly, one of ordinary skill in the art would find it obvious to apply the restenosis inhibiting method of the co-pending application for the reendothelization and vascular endothelial function improving, as in the instant claims, with the expectation that a method that inhibits restenosis also improves the vascular endothelial growth and function.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicant's arguments filed January 23, 2006, have been fully considered but they are not persuasive.

In particular, Applicant's assert that Ungs teaches applying estrogen to the blood vessel walls at a treatment site proximal to or upstream of a stenosis to increase perfusion when PTCA is impracticable. Applicant's assert that Ungs teaches applying estrogen to an uninjured site on a blood vessel to promote generation of other vessels or to increase permeability, but does not disclose (1) administration of estradiol at the injured site, or (2) administering the estradiol for improving reendothelization and vascular function, as recited in the claims.

The Examiner respectfully disagrees. Regarding point (1), Ungs teaches that restenosis following PTCA is a significant problem (see column 1, lines 15-20, in particular.) In other words, the site at which PTCA has been performed, which is necessarily a site at which injury has occurred, is the same site that is susceptible to restenosis. Ungs teaches that administration of estrogen to stenosed dilated region (i.e. the injured site) after PTCA has thus been suggested for the purposes of preventing

restenosis (see column 1, lines 40-53, in particular.) While Ungs does teach that not all regions can be treated with PTCA, Ungs also teaches that it is also desirable to reduce the incidence of restenosis following PCTA or other procedures by providing the estrogen compounds (see column 1, lines 50-65, in particular.) Thus, Ungs teaches administration of the estrogen compound to a site that is susceptible to restenosis, and that has or will experience injury due to techniques such as PTCA or other invasive techniques used to provide the estrogen compound to the stenosed region.

Regarding point (2), it is respectfully pointed out, as discussed above, that the recitation "for improving reendothelization and vascular endothelial function" in claim 1 has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *in re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152 88 USPQ 478, 481 (CCPA 1951.) Furthermore, it is noted that as Ungs teaches administering the same compound via the same method as that instantly claimed, the method of Ungs would necessarily also improve reendothelization and vascular endothelial function, as recited in the claim.

The declaration filed under Rule 132 on January 23, 2006 and signed by Dr. Richard Sean Stack has been fully considered but has not been found persuasive. In particular, the declaration provides statements arguing that it cannot be predicted whether an agent known to prevent or reduce smooth muscle cell proliferation and/or to prevent or reduce blood vessel wall thickening will also promote reendothelization, as recited in the claim (see point 12, in particular.) Thus, the declaration argues that the knowledge that beta-estradiol had an ability to reduce smooth muscle cell proliferation is not sufficient for someone skilled in the art, to predict that beta-estradiol could also promote re-endothelization and endothelial function (see point 14, in particular.)

These arguments are not found persuasive because, as noted above, since Ungs teaches administering the same compound via the same method steps as those instantly claimed, it is considered that the method of Ungs also necessarily improves reendothelization and vascular endothelial function. The fact that applicant has recognized another advantage which would flow naturally from following the teachings or suggestion of the prior art cannot be the basis for patentability when the prior art teaches the invention or when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Applicants furthermore argue that Collins does not teach in situ administration of estradiol. The Examiner notes that Ungs is being relied on to teach in situ administration of estradiol. Collins is begin relied on to teach general ranges of

estradiol that are suitable for various means of administration, to provide general guidance that could be used by one of ordinary skill in the art to determine an appropriate dosage for estradiol in situ, as taught by Ungs. Applicants also argue that Pitha is silent as regards to the reendothelization or vascular endothelia function of estradiol. However, as noted above, Ungs is relied on for a teaching of in situ administration of estradiol, which would necessarily provide the results of improved reendothelization as claimed.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abigail M. Cotton whose telephone number is (571) 272-8779. The examiner can normally be reached on 9:30-6:00, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AMC

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER